

Effect of increasing pressure on excess volumes for cavities in TIP4P water

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Abstract

NPT simulation results on excess volumes computed by the direct method are presented for spherical cavities in TIP4P water. The cavity is created by defining an exclusion volume for water-oxygen. This volume gives a well defined contribution to the excess volume, while the contribution arising from the coupling of all interactions in the system depends on pressure and temperature. This partition is in agreement with Kirkwood-Buff integrals, which provide a useful analysis of excess volumes in terms of the cavity-solvent distribution function. Two main effects of increasing pressure along the isotherm of 298 K are investigated. One refers to comparison of qualitatively different behaviours observed when increasing the exclusion volume at a constant high pressure in comparison to atmospheric pressure. For a nanometric sized cavity, these lead to extrapolate positive and negative adsorption at the cavity surface, respectively at 8000 and 1 atm. A simple radial dependence of excess volumes is able to reproduce these features. The other effect concerns the variation of excess volume under the increasing of pressure in a wide range up to 10000 atm at a fixed cavity radius. Results are presented for two cases corresponding to cavities that can host spherical solutes whose size are as large as a water molecule and slightly larger than a fullerene molecule. Curves obtained by fitting with heuristic models previously tested on pressure dependence of water density enables estimation of the slope. Except for low pressures, these estimated values appear to be generally consistent with those obtained from simulation results of compressibility.

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29 simulations

30 **1. Introduction**

31 The variation of volume in the solvation of a molecule at constant pressure, as well
32 as in chemical reactions and in general processes occurring in a solution, is a quan-
33 tity of fundamental importance within solvation thermodynamics [1, 2, 3, 4, 5].
34 Solutions are generally studied at ambient conditions, but there is great interest in
35 studying processes under different conditions. The effect of pressure on the con-
36 formational stability of a protein in an aqueous solution is a typical example [3].
37 When 1 mol of solute is added to an infinite amount of solution, the variation in
38 volume defines the partial molar volume that is decomposed in an ideal solution
39 contribution and the excess volume [3, 5]. This important intensive variable varies
40 with solution composition. Excess volumes have been mainly obtained experi-
41 mentally [6, 7, 1, 8] rather than from simulations [9, 10, 11, 12, 13, 14, 15, 16, 17],
42 which are generally performed for an infinitely dilute solution.

43 According to the Kirkwood-Buff (KB) theory [18], excess volumes are defined in
44 terms of integrals of pair distribution functions and therefore include a lot of infor-
45 mation on intermolecular affinities. Inversion theory [2, 3, 19, 20] was developed
46 to extract this information from experimental measures of partial molar volumes,
47 while interaction potentials are a fundamental input of molecular simulations from
48 which distribution functions are typical results [21, 22]. In this respect, simu-
49 lations are a useful tool to understand how interactions affect macromolecules
50 properties in aqueous solutions and in complex environments [23, 24, 25]. More
51 recently, given the great interest in biological systems, molecular simulations have
52 been used to compute KB integrals to study cosolvent interactions in aqueous so-
53 lutions with solutes chosen as representative of hydrophilic and hydrophobic sites

on proteins [26]. With the aim of understanding pressure-induced protein denaturation, the different role of these sites has been discussed [27, 28], while volume dependence on pressure has been the object of various studies [29, 17, 30, 31, 32]. A valid alternative approach based on simulations is the direct method [15, 17], whose reliability has been very recently demonstrated in a study of benzene in three solvents at several pressures [32]. The study of the free energy of solvation at various pressures is the basis for a less commonly investigated method that obtains excess volumes from the slope of the fitted curve [17, 32]. Generally, as the curves do not present clear curvature, linear fits are used, and excess volumes are considered almost constant in a wide range of P . On the other hand, the pressure dependence of partial molar volumes has been taken into account for the evaluation of excess compressibility from simulation [17] and experimental data [29]. Unfortunately, the pressure derivative of apparent compressibility has been measured only for very few compounds. Therefore, linear and quadratic descriptions have been assumed for excess volumes. Simulation results have been fitted with quadratic polynomials [17] or using the Tait equation [31], originally applied to pure liquids [33].

This work deals with the effect of increasing pressure on excess volumes of hard-sphere solutes in water at 298 K. The insertion of this simple modeled solute is equivalent to the formation of a cavity [34] and reference is made to the corresponding quantity as cavity excess volumes. In this respect, it is important to recall that there is no size limitation so that cavities can or cannot host a real solute [34] [35].

In the following section, methods to compute excess volumes, either based on

78 simulations or on the pressure derivative of the excess chemical potential, are
 79 briefly outlined. Furthermore, some focus is on volume-derived quantities such
 80 as adsorption at the cavity surface and excess compressibility. Hence, excess vol-
 81 umes from simulations obtained by the direct method [15, 17, 32] are presented
 82 focusing on two main aspects of increasing pressure. Firstly, comparison is made
 83 between very high and atmospheric pressure conditions for the process of scaling
 84 the cavity radius. Secondly, excess volume and excess compressibility are shown
 85 along the isotherm for two specific cavities. Their sizes are appropriate to host
 86 approximately a water molecule and a hypothetical spherical solute slightly larger
 87 than a fullerene molecule. Results are compared with those from KB integrals,
 88 which can be analysed in terms of shell contributions. Finally, some heuristic
 89 expressions to fit simulation results are considered.

90 **2. Calculation**

91 *2.1. Excess Volumes from simulations*

92 In an infinitely dilute solution, solute-solute interactions can be neglected and ac-
 93 cording to the KB theory [18], for a spherical solute the excess volume is directly
 94 related to the radial distribution of the solvent (w) around the solute (s),

$$v_s^* = - \int_0^\infty [g_{sw}(r) - 1] (4\pi r^2) dr \quad (1)$$

95 where the integral is known as the KB integral.

96 As the KB theory has been developed in the gran-canonical ensemble, the solute-
 97 solvent distribution functions should be computed from simulations in this ensem-
 98 ble, even if some studies have shown that the canonical (NVT) [9, 10, 11, 12, 14,

36] and the isothermal isobaric (NPT) [36, 37, 13, 15, 16, 38, 30] ensembles can
 be used without serious problems. These problems can be effectively managed
 [39, 15] by scaling for the correction due to the different asymptotic values of $g(r)$
 in the different ensembles [40, 41]. Nevertheless, irrespective of the statistical
 ensemble, v_s^* from simulations obtained by the KB formula needs to be assessed
 for accuracy because of the truncation of the integrals [11, 15].
 Another method is based on the relation between excess volumes and partial molar
 volumes, v_s , namely:

$$v_s^* = v_s - k_T^0 k_B T \quad (2)$$

where k_B is the Boltzmann constant, T is the temperature and k_T^0 is the solvent
 isothermal compressibility, and in accordance with the thermodynamic definition,
 v_s , the partial molar volume is

$$v_s = \left(\frac{\partial V}{\partial N_s} \right)_{P, T, N_w}, \quad (3)$$

N_s and N_w being the numbers of solute and solvent molecules respectively. Fol-
 lowing this definition, v_s can be computed from simulations in the NPT statistical
 ensemble such as the variation in the average volumes ($\langle V(N_s, N_w) \rangle$) when
 the solute is introduced into the solvent [15]

$$v_s = \langle V(1, N_w) \rangle - \langle V(0, N_w) \rangle. \quad (4)$$

This method is known as the direct method. The term $k_T^0 k_B T$ in Eq. (2) represents
 the thermal contribution of the solute motion to v_s [3], so that if the solute is kept

fixed during the simulation, v_s^* is actually computed by Eq. (4). Alternatively, according to Maghaddam and Chan [17], it can be computed from simulations at a fixed solute position by the expression,

$$v_s^* = \frac{\langle V^2(1, N_w) \rangle}{\langle V(1, N_w) \rangle} - \frac{\langle V^2(0, N_w) \rangle}{\langle V(0, N_w) \rangle}. \quad (5)$$

According to thermodynamics [3, 5], excess volumes can be obtained from a pressure study of the excess chemical potential, μ^* , which expresses how the Gibbs free energy of the system changes as one solute molecule is added to the solvent at a fixed position. Eq. (5) is based on this definition, namely

$$v_s^* = \left(\frac{\partial \mu^*}{\partial P} \right)_T. \quad (6)$$

We recall that excess quantities in this work are defined with respect to an ideal solution in which all molecular interactions are turned off [3, 5], i.e. the ideal gas, as shown in Eq. (2). Thus, μ^* coincides with the pseudochemical potential defined by Ben-Naim [3].

2.2. Decomposition of v_s^* in exclusion volume and ΔV_{AIC}

The formation of a cavity implies the definition of an exclusion volume (V_0) for the motion of solvent centers, from which there arises the natural following decomposition of v_s^* , namely

$$v_s^* = V_0 + \Delta V_{AIC} \quad (7)$$

where ΔV_{AIC} is the difference between v_s^* and the exclusion volume. On the basis of the direct method (Eq. (4)), ΔV_{AIC} can be seen as the variation in volume

133 between the solution and the pure solvent "measured" by the center of the solvent
 134 molecule. This quantity has been defined as a *non-ideal* contribution [11, 15],
 135 with reference to an ideal condition that cannot be confused with the conventional
 136 reference in thermodynamics [3].

137 The exclusion volume has been considered as an *intrinsic* contribution to the
 138 excess volume. However, as already discussed by Matubayasi and Levy [11], his-
 139 torically, the term *intrinsic volume* has been used to indicate the van der Waals
 140 volume of the solute. This is the reference [42] for the non-intrinsic contribution
 141 used by Graziano [43, 44], which does not correspond to the non-ideal contri-
 142 bution used in a previous work [15]. In order to avoid further confusion, in this
 143 work, a new notation is introduced, in which the acronym AIC stands for "all in-
 144 teractions coupled". Hence, ΔV_{AIC} denotes the volume change when water-water
 145 interactions are coupled after an exclusion volume has been defined. This can be
 146 associated with a hard-sphere solute-solvent interaction potential defined by the
 147 contact distance R . In this case, R can be written as the sum of solute and sol-
 148 vent radii. For this reason, the study of cavity formation in water is relevant for
 149 hydrophobic solvation. However, here such an association is not strictly neces-
 150 sary, and one can think in terms of a void contained inside the exclusion region.
 151 Thus, in the present work, only when interpreting the results with reference to the
 152 "intrinsic volume of the solute", was a cavity void volume, V_{cv} , estimated as the
 153 spherical volume of radius $R - r_w$ for an assumed value of r_w , the radius of a
 154 water molecule.

155 The decomposition of v_s^* according to Eq. 7 has been strongly criticized by
 156 Graziano [43, 44], but, once again, it is worthwhile stressing that this is natural

157 for the systems studied in the present and previous works [15, 45, 46]. The main
 158 reason is that the cavity is defined by the exclusion volume. A clarification of the
 159 meaning "non-ideal" when referring to ΔV_{AIC} is given below.
 160 Precisely, for a spherical cavity that excludes a solvent center from the spherical
 161 volume $V_0 = \frac{4\pi}{3}R^3$, according to the KB integral (Eq. (1)), ΔV_{AIC} is zero in
 162 the case of a cavity-solvent correlation function described by a Heaviside step
 163 function, which is expected for a cavity in an ideal gas [47]. Thus, it takes into
 164 account the real cavity-solvent correlation function and is related to the excess
 165 number of solvent molecules at the cavity surface, i. e. at the accessible surface
 166 [45, 48, 46],

$$n_s(R, R) = -\rho\Delta V_{AIC} \quad (8)$$

167 where ρ is the solvent number density. From this quantity, the solvent adsorption
 168 at the same reference surface is readily obtained,

$$\Gamma = \frac{n_s(R, R)}{4\pi R^2}. \quad (9)$$

169 This is an absolute adsorption and strongly depends on the position of the refer-
 170 ence or dividing surface. Originally, this quantity has been introduced within the
 171 thermodynamics of interfaces in the Gibbs approach, which assumes homogenous
 172 phases up to the dividing surface [49]. As a real interface is dishomogenous, an
 173 excess number of molecules is defined for a particular dividing surface. Here, this
 174 surface excess quantity arises from the discrepancy between the real solvent dis-
 175 tribution around the cavity with respect to an "ideal" distribution defined by the
 176 position of the dividing surface, i.e. a Heaviside function.

177 2.3. Solvent and Excess Compressibility

178 An expression for the coefficient of isothermal compressibility can be derived
179 from density in accordance with the thermodynamic definition:

$$k_T^\circ = -\frac{1}{V} \left(\frac{\partial V}{\partial P} \right)_T = \frac{1}{\rho} \left(\frac{\partial \rho}{\partial P} \right)_T. \quad (10)$$

180 This can be compared with volume fluctuation obtained from NPT simulations,
181 namely,

$$k_T^\circ = -\frac{\langle V^2 \rangle_N - \langle V \rangle_N^2}{k_B T \langle V \rangle_N}. \quad (11)$$

182 Similar definitions apply to solutions. How solvent compressibility is affected by
183 the solute can be evaluated directly from the difference in compressibility between
184 the infinitely dilute solution and the pure solvent. When this difference refers to
185 the addition of 1 mol of solute it defines the partial molar compressibility [17].
186 However, as we are much more interested in the pressure derivative of volume
187 variation, we consider what it is known in biophysics as the change in apparent
188 volume compressibility [29]. In the case of a fixed solute position, this quantity
189 refers to the negative pressure derivative of the excess volume,

$$\Delta K_T = - \left(\frac{\partial v_s^*}{\partial P} \right)_T \quad (12)$$

190 and multiplied by the solvent density it corresponds to the excess compressibility
191 defined by Matubayasy and Levy [11]. According to the definition given above,
192 ΔK_T differs from the partial molar isothermal compressibility [17] only for con-
193 tributions of solute translational degrees of freedom, and it can be obtained from

simulation results on system volumes and isothermal compressibilities of pure
solvent and solution,

$$\Delta K_T = k_T < V(1, N_w) > - k_T^\circ < V(0, N_w) > . \quad (13)$$

3. RESULTS AND DISCUSSION

3.1. Computational details

NPT Monte Carlo (MC) simulations were run at 298 K for hard-sphere cavities in 512 TIP4P waters. The center of the cavity was at a fixed position, so that in this case excess volumes were obtained by the direct method (Eq. (4)). To this end, the average volume occupied by the same number of TIP4P waters was used [35]. KB integrals were computed from cavity-solvent rdfs relative to the water-oxygen center. In order to avoid systematic errors due to consideration of the whole volume, including the exclusion volume V_0 , rdfs from Boss [50] were renormalized by scaling them by $< V(0, N_w) > / < V(1, N_w) >$.

3.2. Simulation Results

Two main aspects of the effect of increasing pressure are focused on: (1) the scaling of the cavity radius at a constant high pressure, 8000 atm, shows significantly different features in comparison to the same process at 1 atm; (2) the profile along the isotherm of the excess volume and its slope is shown for two cavities with contact radius of 2.85 and 6.05 Å.

3.2.1. Radial scaling of the cavity: effect of increasing P on ΔV_{AIC} and asymptotic adsorption

Results relative to the scaling of the cavity radius at 8000 atm are collected in Table 1 for v_s^* computed by using the direct method (Eq. (4)) together with compressibility deviation from pure water compressibility, $k_T - k_T^\circ$, and the excess

Table 1: Excess quantities of some hard-sphere cavities in water at 298.15 K and 8000 atm from NPT MC simulations in 512 TIP4P waters. Solutes were at a fixed position. v_s^* obtained by the direct method (Eq. 4). The numbers in parentheses are the statistical uncertainties in the last digit.

r	v_s^*	$\delta v_s^{*(a)}$	$10^6(k_T - k_T^\circ)^{(b)}$	$-\left(\frac{\partial v_s^*}{\partial P}\right)_T^{(c)}$
Å	$cm^3 mol^{-1}$	$cm^3 mol^{-1}$	atm^{-1}	$cm^3 mol^{-1} atm^{-1}$
1.60	0.6(4)	0.0047(5)	-0.19(2)	-0.0014(1)
1.75	1.6(4)	0.0041(5)	-0.17(2)	-0.0012(1)
1.90	2.3(5)	0.0050(5)	-0.21(2)	-0.0015(1)
2.25	5.4(4)	0.0048(5)	-0.20(2)	-0.0014(1)
2.55	10.0(4)	0.0047(5)	-0.19(2)	-0.0013(1)
2.85	17.7(4)	0.0039(5)	-0.16(2)	-0.0009(1)
3.30	33.6(4)	0.0030(5)	-0.12(2)	-0.0004(1)
3.65	51.2(4)	0.0038(5)	-0.16(2)	-0.0004(1)
4.05	78.5(4)	0.0022(5)	-0.09(2)	0.0005(1)
4.45	112.9(4)	0.0029(5)	-0.11(2)	0.0007(1)
5.05	182.4(4)	0.0031(5)	-0.13(2)	0.0017(1)
5.45	242.2(4)	0.0013(5)	-0.05(2)	0.0031(1)
6.05	353.7(4)	0.0052(5)	-0.21(2)	0.0035(1)

(a) systematic deviation of values obtained by Eq. 4 from values obtained by Eq. 5 evaluated as $(k_T^\circ - k_T) * k_B T$ (see Eqs. 11-13 of Ref. [17])

(b) k_T and k_T° from volume fluctuations (Eq. 11).

(c) obtained by Eq. 13.

Table 2: Excess volumes (v_s^*) at 1 atm and 298.15 K for some cavities in water and effect of increasing the pressure up to 8000 atm (Δv_s^*). Results obtained by Eq. 4 from NPT MC simulations in 512 TIP4P waters where oxygens were excluded from the spherical volume of radius R (V_0). The additional contribution from correlations following the coupling of all interactions in the system (ΔV_{AIC}) is given for the system at 1 atm. Also contributions relative to the decomposition with reference to spherical volume of radius $R - r_w$ (V_{cv}) are for systems at atmospheric pressure. The numbers in parentheses are the statistical uncertainties in the last digit. Radii in Å and volumes in cc/mol.

R	$v_s^*^{(a)}$	$\Delta v_s^*^{(b)}$	V_0	$\Delta V_{AIC}^{(a)}$	$R - r_w^{(c)}$	$V_{cv}^{(d)}$	$v_s^* - V_{cv}^{(a)}$
2.85	24.9(7)	-7.2(8)	58.4	-33.5	1.47	8.0	16.9
3.30	47(3)	-13(3)	90.7	-44	1.92	17.9	29
4.05	108(2)	-29(2)	167.6	-60	2.67	48.0	60
4.45	162(2)	-49(2)	222.3	-60	3.07	73.0	89
5.05	252(1)	-69(1)	324.9	-73	3.67	124.7	127
5.45	335(1)	-93(1)	408.3	-73	4.07	170.1	165
6.05	485(2)	-131(2)	558.6	-74	4.67	256.9	228

(a) $P = 1$ atm

(b) $\Delta v_s^* = v_s^*(8000 \text{ atm}) - v_s^*(1 \text{ atm})$

(c) $r_w = 1.38 \text{ Å}$

(d) spherical volume of radius $R - r_w$

217 volume compressibility defined by Eq. (12) and computed by Eq. (13). Discrep-
218 ancies with respect to Eq. (5), δv_s^* (third column), were derived from $k_T^\circ - k_T$.
219 These are systematically positive and very small with regard to statistical uncer-
220 tainties on v_s^* . Similar results have been obtained for methane in water [17]. Data
221 of ΔK_T (last column of Table 1) obtained from Eq. 13 give interesting depen-
222 dence on the cavity radius for the slope of the excess volume (Eq. (12)). Ac-
223 cording to these results, at 8000 atm, the excess volume of a specific radius can
224 increase or decrease with increasing pressure depending on whether the radius is
225 less or greater than about 3.9 Å, for which a stationary point may be expected.
226 Throughout the range, excess volumes at 8000 atm are generally significantly

Figure 1: Dependence on the cavity radius (R) at 1 *atm* (black filled circles) and 8000 *atm* (blue filled squares) for the excess volume (v_s^*) obtained by the direct method (Eq. 4) from NPT MC simulations at 298 K. The green curve represents the excuded volume (V_0) while the red line is the volume of the cavity void (V_{cv}), i.e. the spherical volume of radius $R - r_w$.

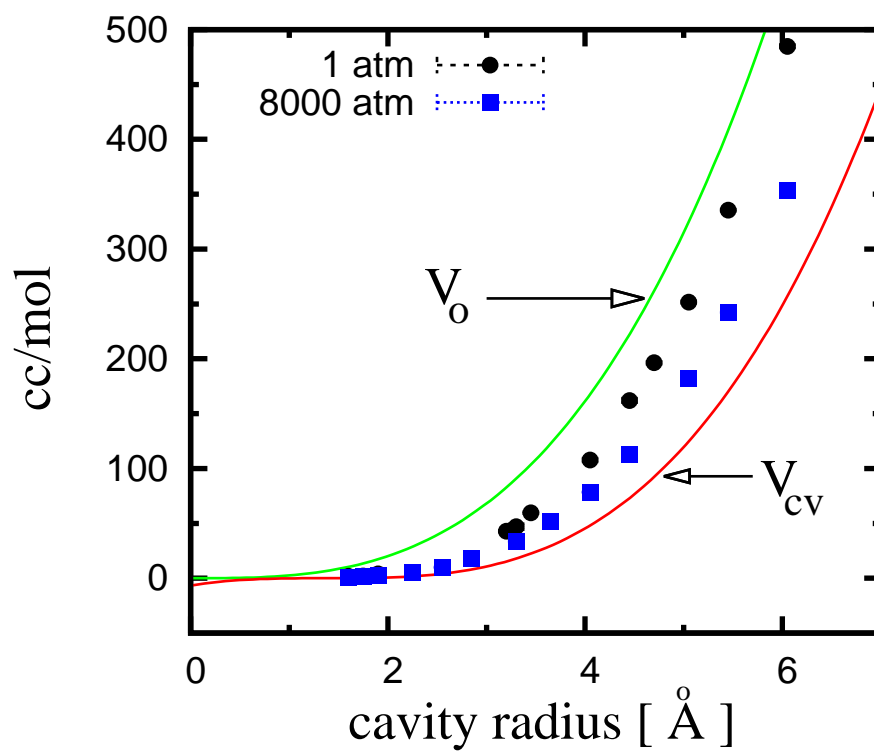
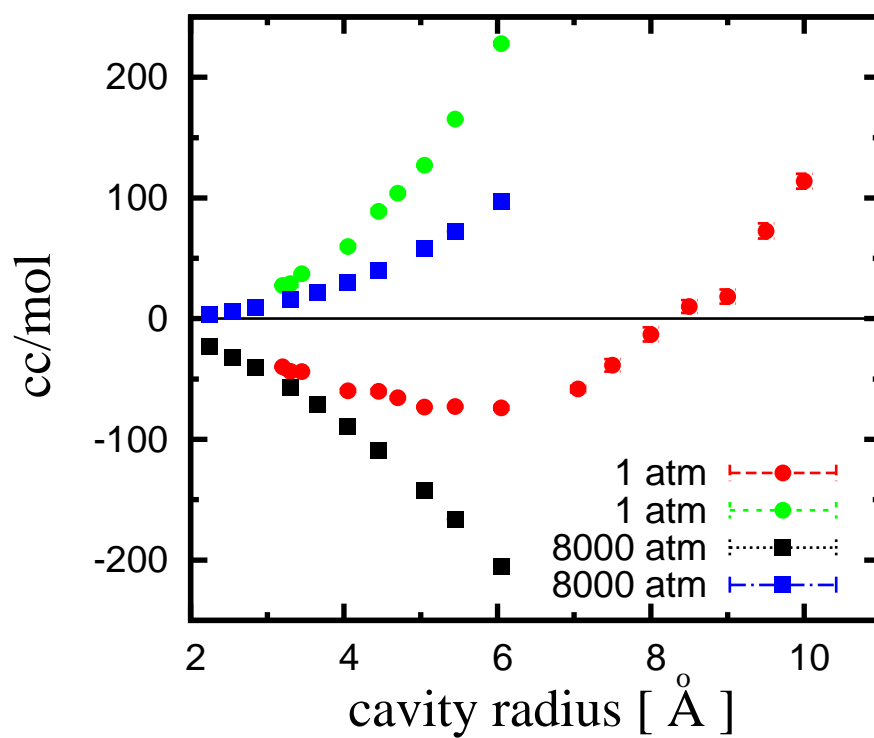


Figure 2: Dependence on the cavity radius (R) of ΔV_{AIC} (Eq. 7) at 1 atm (red filled circles) and 8000 atm (black filled squares). Contributions to the excess volume obtained as the difference $v_s^* - V_{cv}$ are also shown at 1 atm (green filled circles) and 8000 atm (blue filled squares). In both decompositions, v_s^* were computed by the direct method (Eq. 4).



227 reduced with respect to those obtained at atmospheric pressure which were pre-
 228 sented and discussed in a previous work [15]. This is shown in the third column
 229 of Table 2 and in Fig. 1. For an excluding cavity radius R up to 6.05 \AA , results
 230 of both pressures are in between the volume of the cavity void (V_{cv}) and the ex-
 231 clusion volume (V_0). Thus, in the range plotted in the figure, results come up to
 232 Graziano’s expectations [43, 44], which have been based on empirical schemes
 233 employed in rationalizing partial molar volumes of various solutes [38]. For more
 234 discussion on this point, see also Section 3.3.1. The decomposition of v_s^* with
 235 respect to V_0 or V_{cv} yields rather different contributions which for both pressures
 236 are plotted in Fig. 2. For R within 6.05 \AA , values at atmospheric pressure are also
 237 reported in the fourth and in the last column of Table 2, respectively. In this range,
 238 at both pressures, even the sign of the two ”non-intrinsic” contributions is differ-
 239 ent. This is not surprising, as the cavity void is much smaller than the exclusion
 240 volume.

241 For cavities at 1 *atm* [15, 51], comparison between methods to compute v_s^* re-
 242 vealed the importance of ΔV_{AIC} ($v_s^* - V_0$), as this *non - ideal* contribution is
 243 related to solvent correlation around the cavity. The scaling of cavity radius pro-
 244 duces interesting features regarding the radial profile of this quantity, with a crit-
 245 ical point between 5 and 6 \AA and an inversion of sign between 8 and 10 \AA (Fig.
 246 2). Although in quantitative disagreement in this range, methods based on sim-
 247 ulations give the same trend of results with R , while methods based on models
 248 [15, 30], can or cannot reproduce such behaviour. This mainly shows a positive
 249 ΔV_{AIC} for nanometric-sized cavities to which there corresponds a negative ad-
 250 sorption at the accessible reference surface [45, 46]. This can be justified on the

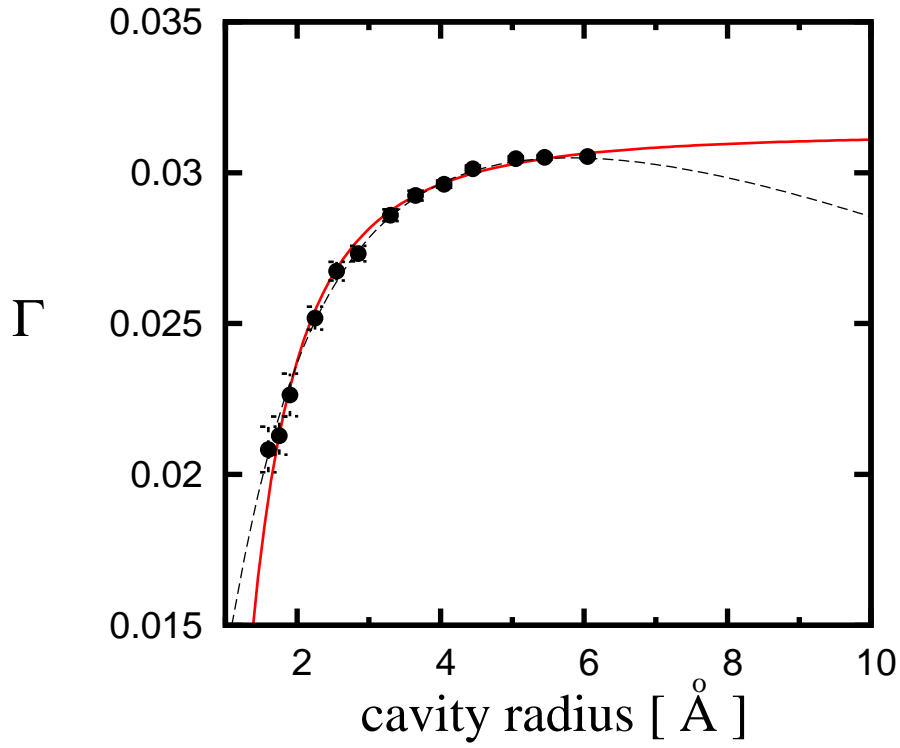
251 basis of conditions near to vapor-liquid equilibrium, and transition to positive ad-
 252 sorption appears reasonable when increasing pressure [30]. This view has been
 253 proven valid for cavities in water [15, 45, 30], and in LJ liquids [30]. Thus, fitting
 254 ΔV_{AIC} against the cavity radius at atmospheric pressure [45], negative adsorp-
 255 tion at the cavity accessible surface was extrapolated for nanometric and larger
 256 cavities. At the same time, the sign of this quantity was confirmed by examining
 257 two possible evolutions of the cavity-water rdf in the limit of a very large cav-
 258 ity. The extrapolated profile was compared with gas/liquid and wall/liquid density
 259 profiles, showing that it is sharper, but with a thickness similar to that obtained for
 260 a phobic wall. In the same limit, LCW [52] theoretical results obtained by Huang
 261 and Chandler [53] have shown a density profile with a thickness very similar to
 262 those obtained from simulations of the gas/liquid interface obtained with TIP4P
 263 and SPC/E models. Hence, as a consequence of a more dewetted density profile,
 264 adsorption at the accessible dividing surface is more negative than that extrapo-
 265 lated from our data [15, 45]. For a detailed comparison of cavity-water rdfs see
 266 [45]. Such a discrepancy has already been evident for a cavity radius R of 100 Å.
 267 However, the opposite occurs for R less than 20 Å, at which profiles are very sim-
 268 ilar. On the basis of this, when inserting these rdfs in the KB integrals a change
 269 of sign for ΔV_{AIC} is also expected for LCW theoretical results, even if this likely
 270 occurs at R between 8 Å and 20 Å .
 271 In the previous work [15], it was shown that SPT and BMCLS never predict such a
 272 change of sign. This has been claimed by Graziano [43, 44] as a fundamental point
 273 in contrast with conclusions of previous works [15, 45]. However, as already noted
 274 [15], when enlarging the cavity radius, SPT disagrees with simulation results also

275 for thermodynamic quantities, such as the enthalpic and the entropic contribution
 276 to the change of free energy associated with the cavity formation in TIP4P water
 277 [54]. To be precise, these simulation results indicate that for R larger than 4
 278 Å, the cost of cavity formation is dominated by a positive variation of enthalpy.
 279 This is in line with ideas expressed in the literature for the process at ambient
 280 conditions [55]. The change of sign of ΔV_{AIC} is clearly related to dewetting
 281 and a nanometric sized cavity is considered dewetted. It seems well founded
 282 that around 8-10 Å there is the crossover between "wet" and "dewetted" cavities,
 283 which is accompanied by a change in the thermodynamic of the process [55].
 284 Turning to the scaling of the cavity radius at 8000 atm, ΔV_{AIC} (Fig. 2) shows
 285 a monothonic decrease and is expected to be always a negative quantity, and a
 286 positive adsorption of water-oxygen centers is obtained at the cavity surface (Fig.
 287 3). As for the contact value of rdf observed at this pressure [15], it seems reason-
 288 able to consider that at ~ 6 Å also this quantity practically converges to a constant
 289 value. On the basis of this assumption, the asymptotic value of adsorption would
 290 be positive in contrast with that predicted for the scaling at 1 atm. This very
 291 different behaviour was observed in conjunction with very "wet" cavity surfaces
 292 at high pressure [35]. Therefore, KB integrals provide a useful interpretation of
 293 these results (see Section 3.2.2).
 294 The effect of increasing pressure on the thermodynamics of cavity formation re-
 295 quires further investigation and is beyond the scope of this work. However, it
 296 is worthwhile mentioning results from the analysis made by Kalinichev et al.
 297 [56] on pure water described by the same intermolecular potential used in this
 298 work (TIP4P). They have observed that the structure and the energy of hydrogen

299 bonds is only slightly affected by compression up to 10000 atm along the 298
 300 K isotherm. In addition, a redistribution of interaction energies has been found,
 301 with increase in the number of pairs with repulsive and "weakly-bonded" inter-
 302 actions. This suggests that the unfavourable entropic contribution due to packing
 303 might be much more important when creating the cavity at high pressure. Under
 304 the assumption that this is the dominant effect, SPT would be able to describe the
 305 properties of cavities in water. However, it was found [35] that SPT gives incor-
 306 rect radial scaling of the contact value of the cavity-oxygen rdf for cavities with
 307 excluding radii R up to $\sim 6 \text{ \AA}$. In contrast, at larger radii a strong reduction of the
 308 the parameter defining the size of a water molecule is necessary to converge to the
 309 curve that correctly describes simulation results. From this it may be inferred that
 310 the packing effect would be dominant for nanometric and larger cavities, differ-
 311 ently from what has been supposed at atmospheric pressure [57, 58, 59, 60].
 312 At the same time, at high pressure, the energetic contribution can be supposed
 313 to be less unfavourable than at atmospheric pressure. Nevertheless, this needs
 314 to be ascertained by a direct analysis on the cavity-water system. Certainly, in-
 315 stead there is a striking effect on the variation of enthalpy included in the variation
 316 of the pressure-volume term. It is well known that enlarging the cavity at atmo-
 317 spheric pressure [55, 35], the pressure-volume term is negligible up to R of several
 318 nanometers. In contrast, for the same process at 8000 atm, even a variation of the
 319 excluding cavity radius R from $\sim 4 \text{ \AA}$ to $\sim 6 \text{ \AA}$ would involve a pressure-volume
 320 increase of some hundreds of KJ/mol, which is likely greater than the variation in
 321 energy [54].

322

Figure 3: Adsorption Γ (\AA^{-2}) at the cavity surface versus the cavity radius (\AA) obtained by using the direct method to compute v_s^* (points with error bars). Lines represent results from fitting v_s^* with Eq. 14 (dashed black lines) and with Eq. 15 (red line).



3.2.2. Radial scaling of the cavity: analysis of ΔV_{AIC} from KB integrals

For cavities at 8000 atm, ΔV_{AIC} obtained by using the direct method is compared in Fig. 4 with results from KB integrals. As in the case of cavities at 1 atm, these methods based on simulations agree on the radial dependence of this quantity and generally show small discrepancies, even though these were found to be significant for a nanometric cavity. Approximations based on a different truncation of the integral are possible. Among these are hydration shell models [11, 36, 15] corresponding to the truncation at the first, second, and, when possible, the third minimum of the rdf. The results shown in the figure were obtained by using the alternative model proposed in [15]. This approximation can be justified by the oscillatory behaviour of the integral versus the truncation radius, and it estimates ΔV_{AIC} at the average value between the distances corresponding to the last critical points of the integral.

Interestingly, as depicted in Fig. 5 for different cavity radii R , the integrals show very close positions for critical points when plotted versus $R_t - R$, R_t being the truncation radius. At the first minimum of each curve, the integral includes contributions due to centers closer to the center of the cavity, more precisely, those with distances up to that at which the cavity-solvent rdf crosses the ideal correlation (see Section 2.2). All the other critical points of curves similarly correspond to distances of water-oxygens from the center of the cavity at which $g(r) = 1$. Mainly, the damped oscillating curves differ for amplitude, which is greater for larger cavities. At each level of approximation, ΔV_{AIC} is negative, as was observed at atmospheric pressure for R up to 9 Å, while for larger cavities, this was found only at the first shell approximation level. Indeed, the inclusion of the

347 second shell contribution was determinant in the inversion of sign. For a more
 348 detailed analysis see Ref. [15].
 349 It can be noted (see Fig. S1 in Supplementary Data (SD)) that the first hydration
 350 shell gives a large contribution to ΔV_{AIC} . Discrepancies with respect to the best
 351 estimated values can be negative or positive and are within 10-25 %. However,
 352 a high pressure determines very well defined shells that bring to very significant
 353 negative contributions also from the second peak of the rdf. Still more impor-
 354 tant than that found at atmospheric pressure [15, 51] is that, even if more distant
 355 solvent centers are less correlated to the cavity center, the corresponding smaller
 356 deviations of $g(r)$ from 1 have weights in the integral that increase as $4\pi r^2$.
 357 In the NPT ensemble, the excess volume is a local quantity [11, 36, 15, 5], i.e.
 358 molecules very far from the center of the solute do not give any contribution.
 359 This applies also to cavities in water and is clearly shown by examining δV_{AIC} ,
 360 which represents $\Delta V_{AIC}(R_t)$ normalized to the average number of molecules ly-
 361 ing within the truncation radius R_t . As an example, in Fig. 6, profiles are shown
 362 for some cavity radii at 1 and 8000 atm. The quantity is very sensitive to the
 363 cavity-solvent correlation and is reduced to a small value for molecules which are
 364 three molecular diameters away from the cavity surface. The striking effect of in-
 365 creasing pressure is particularly evident for the larger cavity studied at 8000 atm,
 366 with a significant increase of the negative contribution for solvent centers closer
 367 to the cavity center. This is a consequence of a very different cavity-oxygen rdf,
 368 which has higher contact values [45, 35] at 8000 atm. The arrows in the figure
 369 indicate the direction of increasing R , which is opposite at the two pressures.
 370 When this is done at atmospheric pressure, the cavity surface becomes less wet

371 and δV_{AIC} is less negative for centers closer to the cavity. For a nanometric cav-
 372 ity, this quantity is positive as a consequence of $g(R) < 1$. Nevertheless, when
 373 increasing the truncation radius, it becomes negative and then again positive. The
 374 first change in sign is due to contributions related to the peak of the rdf, which in
 375 this case is shifted with respect to the contact distance. When the truncation radius
 376 coincides with the first minimum of the rdf, δV_{AIC} is small and negative, while
 377 at a slightly larger R_t it becomes positive. In all other cases shown, which corre-
 378 spond to cavities for which the excess volume is less than the exclusion volume,
 379 the contribution per molecule is instead always negative.

380 3.2.3. *Dependence on pressure of excess volumes and excess compressibility*

381 Here, simulation results of v_s^* and its slope along the isotherm (298 K) are dis-
 382 cussed for two specific cavities. These can host a spherical solute approximately
 383 as large as a water molecule ($R = 2.85 \text{ \AA}$) and slightly larger than a fullerene
 384 molecule ($R = 6.05$).

385 Data of v_s^* obtained by the direct method at several values of pressure along the
 386 isotherm are plotted in Fig. 7 (a) and Fig. 8 (a). In both cases this quantity mainly
 387 decreases when pressure increases, even if there is a strong dependence on cavity
 388 size regarding the range of variation. Over 10000 atm, this range changes from
 389 about 10 to 130 cc/mol in passing from a contact radius of 2.85 to 6.05 \AA . These
 390 data suggest that profiles of v_s^* along the isotherm should have a negative slope and
 391 this is much larger for the larger cavity. This implication is confirmed by slopes
 392 obtained by Eq. (13) from simulation results of isothermal compressibilities of
 393 pure water and the solution of hard-sphere solutes (see Fig. 7 (b) and Fig. 8 (b)).
 394 Looking more in detail, it can be noted that the decreasing of v_s^* along the

Figure 4: Dependence on the cavity radius (R) at 8000 *atm* for ΔV_{AIC} , the non-ideal correlation contribution to the excess volume (v_s^*). NPT Monte Carlo simulation results from the direct method (Eq. 4) (filled circles) are fitted with (Eq. 15) and compared with results from KB integrals (Eq. 1).

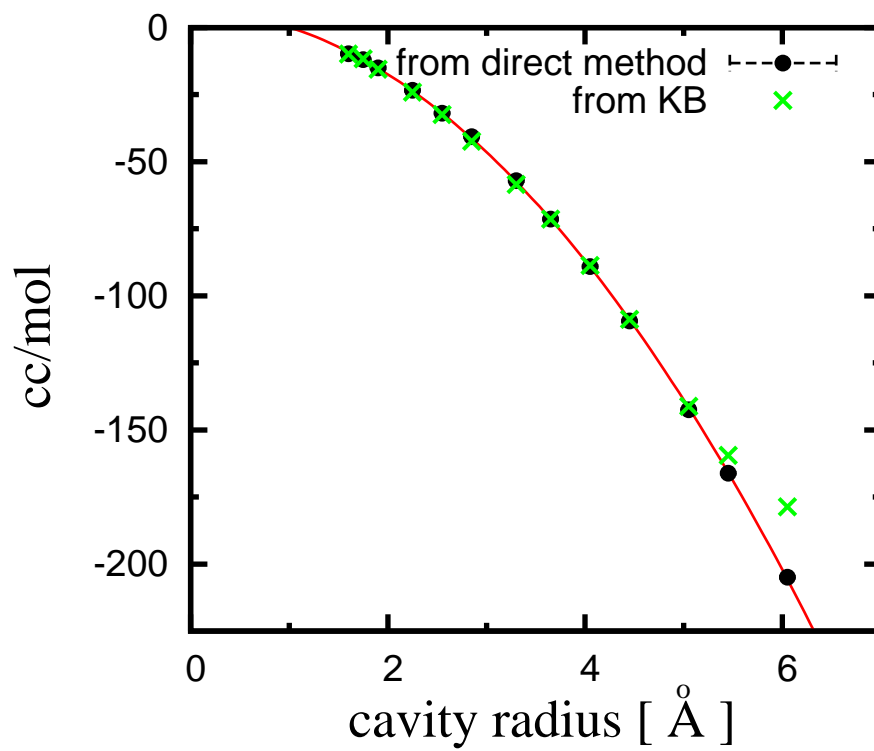


Figure 5: Results of ΔV_{AIC} at 8000 atm from the KB integral ($\Delta V_{AIC} = -KB - V_0$) as function of the truncation radius (R_t) in the integral plotted versus $R_t - R$ for cavity radii (R) from 1.6, to 6.05 Å. The arrow shows the direction of increasing R . For the largest cavity, points give values relative to the first (A), the second (B) and the third (C) shell approximations, and the value read at the average between the distances corresponding to the last critical points of the integral (D).

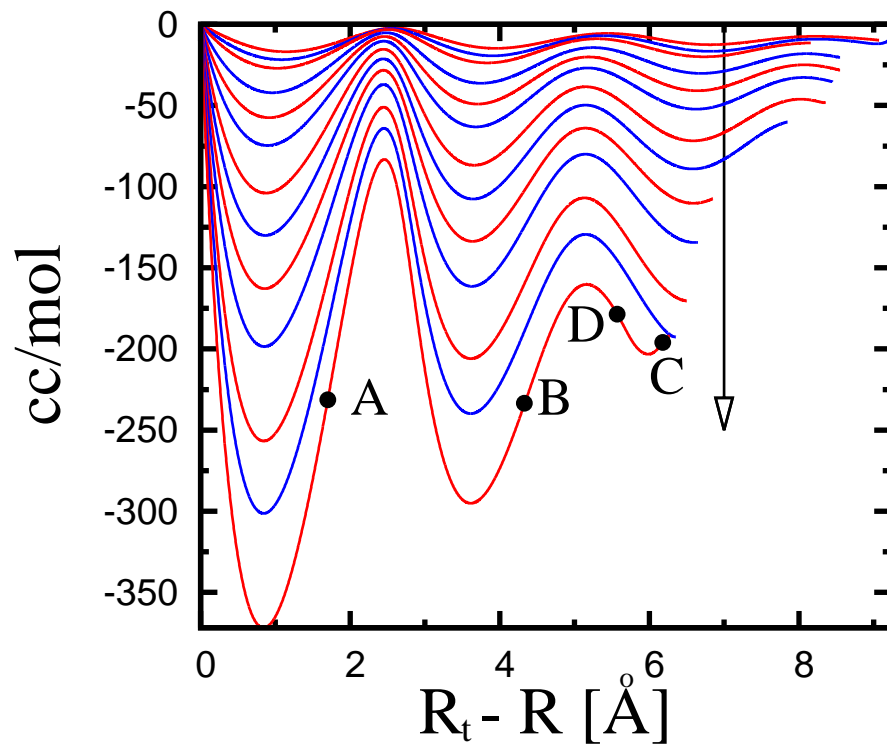
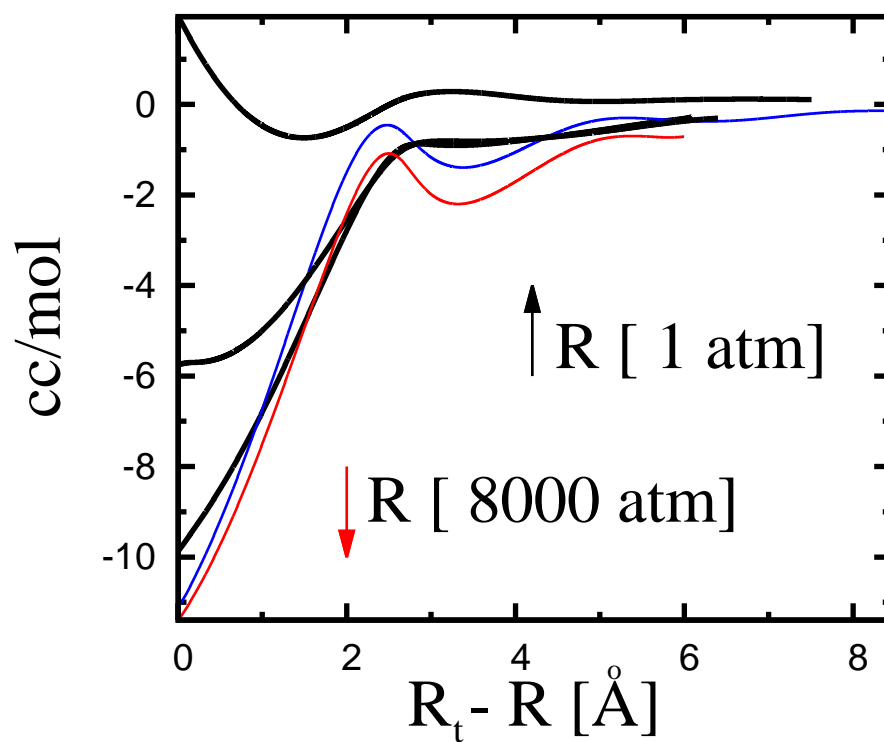


Figure 6: Pressure effect on δV_{AIC} for for some cavity radii as a function of $R_t - R$, being R_t the truncation radius in the KB integral and R the cavity radius. Results at 1 atm are represented by black lines ($R = 2.85 \text{ \AA}$, 6.05 \AA , 10 \AA). Results at 8000 atm are represented by blue ($R = 2.85 \text{ \AA}$) and red ($R = 6.05 \text{ \AA}$) lines. The two arrows indicate the opposite directions of increasing R .



395 isotherm is not linear and presents, in both cases, a strong variation of slope in
 396 the limit of low pressure. However, for $R = 2.85 \text{ \AA}$, dependence on pressure
 397 appears non-monothonic, even if it is difficult to ascertain the existence of critical
 398 points from the data. Also, results from Eq. (13) give positive slopes at 6000
 399 and 8000 atm and this can indicate some possible inversion of slope's sign in the
 400 curve (Fig. 7 (b)). On the contrary, for $R = 6.05 \text{ \AA}$ slopes are negative in the
 401 same range, even if much smaller than values obtained in the limit of low pres-
 402 sure. This behaviour is in line with what is mentioned in Section 3.2.1 regarding
 403 the dependence of ΔK_T on the cavity radius when pressure is 8000 atm (Tab. 1).
 404 Finally, some consideration must be taken of possible systematic errors in simu-
 405 lation results of compressibility of pure water, for data at 200 and 6000 atm [35].
 406 Moreover, in these two cases, statistical uncertainties were greater than for other
 407 pressures. In particular, k_T^0 at 200 atm is underestimated. This error brings about
 408 overestimated values of ΔK_T , which are out of the range shown in the figures.

409 3.3. Describing how v_s^* depends on cavity radius and pressure

410 Models which have some theoretical foundation to compute v_s^* are based on the
 411 pressure derivative of the pseudochemical potential (Eq. (6)). The particular
 412 features of the radial scaling of ΔV_{AIC} observed in simulation results at 1 atm
 413 are predicted neither by the approximate Scaled Particle Theory (SPT) [61] nor
 414 by BMCLS [62, 63] expressions [15]. However, these quantities are well repro-
 415 duced when μ^* is described by the revised SPT expression [30]. This section deals
 416 instead with simple heuristic models in order to fit simulation results of excess
 417 volumes.

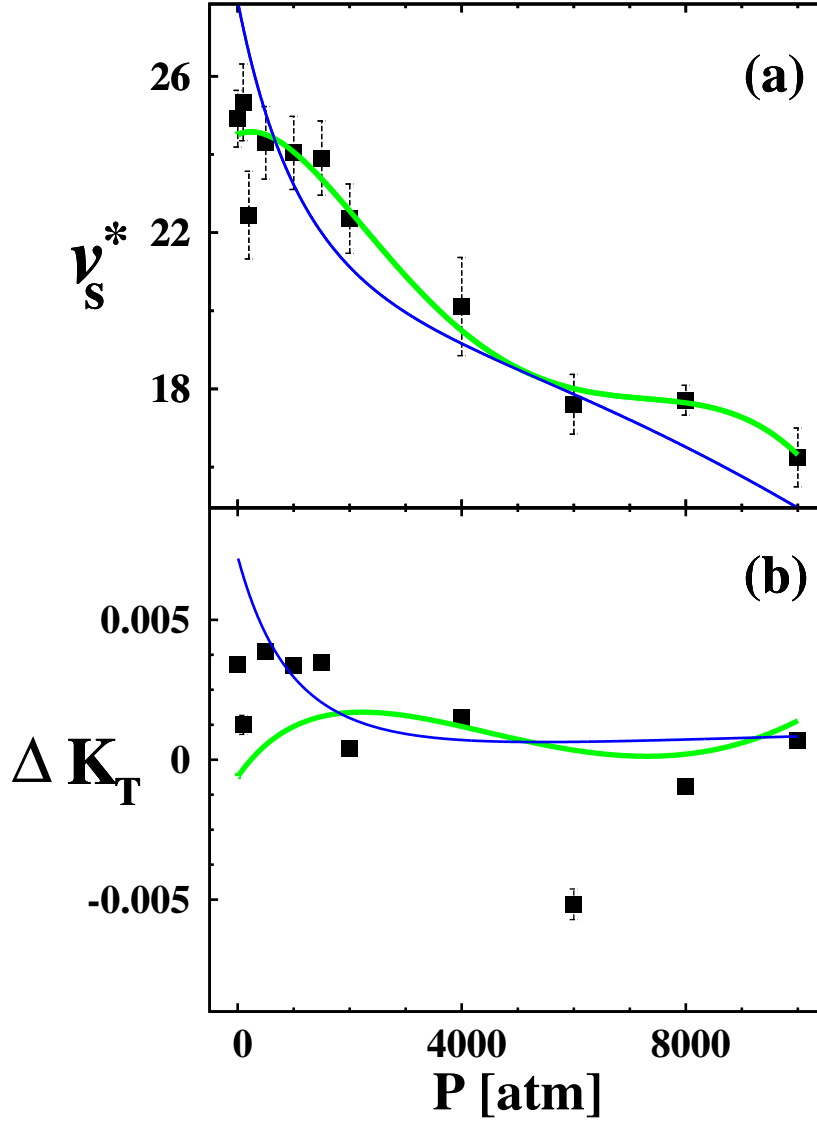


Figure 7: (a) Simulation results of v_s^* (cc/mol) computed by the direct method (points with error bars) for a cavity radius of 2.85 Å in TIP4P water plotted versus pressure. Lines represent results from fits of quantities related to average accessible volumes in pure water and in the solution with Eq. (16) (line green) and with Eq. (17) (line blue). (b) The negative pressure derivative of v_s^* (cc/(mol atm)) vs pressure obtained from simulation results of volumes and compressibility Eq. (13) (points with error bars) and from Eq. (12) using expressions derived from Eq. (16) (line green) and Eq. (17) (line blue).

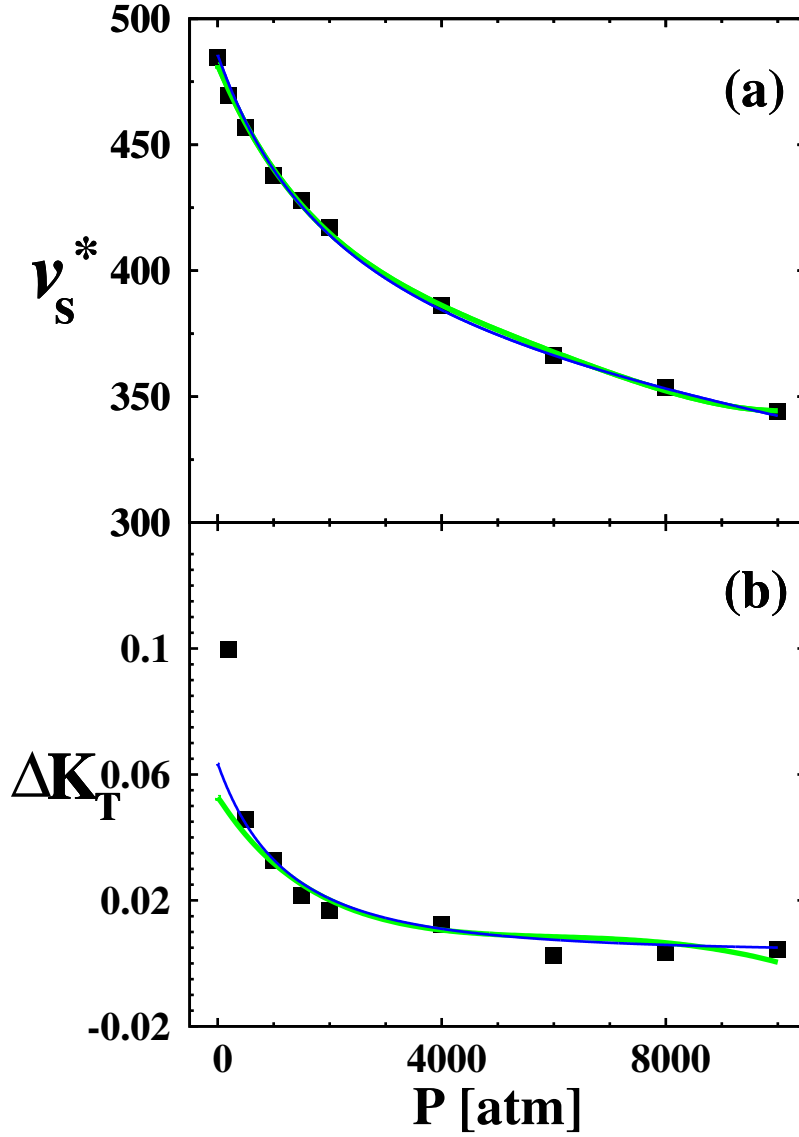


Figure 8: (a) Simulation results of v_s^* (cc/mol) computed by the direct method (points with error bars) for a cavity radius of 6.05 Å in TIP4P water plotted versus pressure. Lines represent results from fits of quantities related to average accessible volumes in pure water and in the solution with Eq. (16) (line green) and with Eq. (17) (line blue). (b) The negative pressure derivative of v_s^* (cc/(mol atm)) vs pressure obtained from simulation results of volumes and compressibility (Eq. (13)) (points with error bars) and from Eq. (12) using expressions derived from Eq. (16) (line green) and Eq. (17) (line blue).

418 *3.3.1. Fitting v_s^* against cavity radius at constant pressure*

419 At constant pressure, the radial dependence of ΔV_{AIC} , and namely v_s^* can be
 420 described by a very simple expression that is able to fit both, data at 1 atm and at
 421 8000 atm, namely

$$v_s^* = C \left(\frac{4}{3} \pi \right) (a + b R)^3 \quad (14)$$

422 where C is a conversion factor from \AA^3 to $\text{cm}^3 \text{mol}^{-1}$. Precisely, at 1 atm, $a =$
 423 $-0.98(6) \text{ \AA}$ and $b = 1.12(2) \text{ \AA}$ were found in our previous work [48, 46] while,
 424 at 8000 atm, $a = -1.018(5) \text{ \AA}$ and $b = 1.0274(1) \text{ \AA}$ were found for the results
 425 presented in this work and shown in Table 1. However, Eq. (14) does not fulfill
 426 the requirement of a constant adsorption at infinity [64], except in the case of
 427 $b = 1$. For this reason in previous works [45, 48, 46], by scaling to further larger
 428 radii, a quadratic polynomial was adopted for n_s and consequently for ΔV_{AIC} .
 429 This model inserted in Eq. (7) gives

$$v_s^* = C \left(\frac{4\pi}{3} R^3 + a_2 R^2 + a_1 R + a_0 \right). \quad (15)$$

430 It can be emphasized that a constant value of adsorption at the accessible dividing
 431 surface in the limit of an infinite radius is consistent with convergence of the con-
 432 tact value of $g(r)$ to $P/(\rho K_B T)$ in the same limit. Both convergence requirements
 433 are fulfilled also by Eq. (14) when, for $b = 1$, it reduces to a particular case of Eq.
 434 (15). Adsorption from simulation results at 8000 atm (Fig. 3) appears to converge
 435 fast to a positive constant value. Both equations here discussed fit well the data,
 436 but lead to very different extrapolations outside the range (see also Fig. S2 in SD).
 437 With $b = 1$, Eq. (14) reduces to the expression [42] that has been used for the ”
 438 cavity volume” deduced using SPT from experimental excess volumes of solutes

439 in water [65]. In order to obtain the so called "border thickness" parameter [65,
 440 44], R is written as the sum of two radii, i.e. $R = r_c + r_w$, for a chosen value
 441 of r_w (1.38 Å), whose pressure dependence was neglected. At 8000 atm, the
 442 optimal value of parameter a is -0.876 Å that corresponds to a "border thickness"
 443 of 0.505 Å. The performance of the fitting is not as good as that obtained when
 444 also parameter b is optimized. This is still more evident at 1 atm, for which the
 445 "border thickness" falls in the range between 0.72 and 1.38 Å, when fitting data
 446 in different ranges of R . Simulation results interpreted with this model clearly
 447 indicate that this parameter increases with the size of the cavity, at atmospheric
 448 pressure. Similar results have been obtained from the "cavity volume" extracted
 449 from experimental excess volumes of various small solutes and some globular
 450 proteins [65, 38, 66].
 451 However, according to Chalikian and coworkers [66], the "border thickness" should
 452 reach a plateau of 1 Å for solutes with van der Waals radii of ~ 7 Å ($R \sim 8.4$ Å),
 453 in contrast with the larger value obtained from simulations of cavities in TIP4P
 454 water [15]. Graziano [44] argued that systematic errors in the simulations of the
 455 largest cavities [15] can explain such disagreement with SPT interpretation of ex-
 456 perimental data. Even if errors in simulations cannot be ruled out [15, 59, 45, 46],
 457 this view does not appear well founded for the following reasons: (1) the compar-
 458 ison between simulation results and those extracted from experimental data is not
 459 consistent; (2) the lack of experimental data on larger spherical solutes; (3) the
 460 "border thickness" is defined within an empirical scheme. Moreover, the overes-
 461 timated compressibility of TIP4P has been indicated as a possible source of errors
 462 in simulations, even though, one should prove that the box containing the cavity

is much more affected by this problem than the box of pure water. At the same time, one should explain why excess volumes from SPT were found qualitatively similar when using instead of experimental values, those of the TIP4P water [15]. Very recently, simulation results on repulsive spherical solutes in water at 1 atm have confirmed that the "border thickness" increases with the solute size, and that this is consistent with dewetting [67]. However, a smaller increase has been observed when also attractive solute-water interactions have been coupled. Values from simulation results of hydrated non-polar molecular solutes obtained by Chalikian and coworkers [66] have been found in between. In these cases, according to Ashbaugh et al. [67], a larger "border thickness" does not indicate dewetting, but is related to the assumed spherical shape when calculating the van der Waals volume of these solutes.

3.3.2. *Fitting v_s^* against pressure at fixed cavity radius*

Simple models for $v_s^*(P)$ can follow from the two expressions proposed in a previous work [35] to fit the inverse of number density. Both have been found able to give at the same time a good description of TIP4P water and experimental data. One is linear in constant parameters, t_0, t_1, t_2, t_3 and t_4 ,

$$\frac{1}{\rho(P)} = t_0 + t_1 P + t_2 P^2 \ln(P/P_0) + t_3 P^{2.5} + t_4 P^3 \quad (16)$$

where P_0 is the unity used for pressure, here 1 atm, while the other can be seen as a modified Tait expression,

$$\frac{1}{\rho(P)} = \frac{1}{\rho_0} + \frac{(ab - c) \ln(bP + 1) + bcP}{b^2} \quad (17)$$

482 where the constant parameters are ρ_0 , a , b and c . These expressions can be used
 483 for pure water and for the corrected number density in the system containing the
 484 cavity, i.e. to fit $\langle V \rangle / N_w$ and $(\langle V \rangle - V_0) / N_w$ respectively, N_w being the
 485 number of waters in the box of simulations . Thus, the same functional form
 486 can describe accessible volumes from which v_s^* can be obtained, as well as its
 487 pressure derivative at a fixed cavity radius. Furthermore, because of the linearity
 488 with respect to parameters, Eq. (16) can also be used to fit this quantity directly.
 489 In Fig. (7) and Fig. (8), results from the heuristic expressions above are shown for
 490 contact radii of 2.85 and 6.05 Å respectively. Overall, their performance can be
 491 judged relatively and reasonably good, given the large range of pressure consid-
 492 ered. In particular for the smaller cavity, Eq. (16) performs better than Eq. (17),
 493 as already observed for pure water when interactions are described by the TIP4P
 494 model potential [35]. Slopes of the curves qualitatively differ (Fig. 7) within the
 495 limit of low pressure. In this range simulation results of excess volumes appear
 496 scattered even if with values which are close to one another approximately within
 497 statistical uncertainties. This could indicate the possible existence of a maximum
 498 for v_s^* , as predicted by Eq. (16) ($P \simeq 225 \text{ atm}$). For methane in TIP4P, at the
 499 same temperature, a similar trend was observed when pressure is raised, with a
 500 clear decreasing of the excess volume only for pressures greater than 1000 *atm*.
 501 However, ΔK_T computed from simulation results of compressibility and average
 502 volumes seem to indicate that v_s^* generally decreases except for between 6000
 503 and 8000 *atm*. On the contrary, for the larger cavity, in Fig.8, the decreasing of
 504 this quantity appears very clearly in all the range of pressure, and both heuristic
 505 expressions predict slopes which are consistent with simulation results from Eq.

(13). Nonetheless, it is evident that curves can differ for relatively small quantities, which are generally within statistical uncertainties on v_s^* , but slopes can be quite different. This is in line with the general problems expected when computing derivatives.

4. CONCLUSIONS

In this work, NPT MC simulation results of excess volumes computed by the direct method are presented for hard-sphere cavities in TIP4P water. Two main effects of increasing pressure at 298 K are investigated. The first depicts a very different behaviour of the non-ideal correlation contribution, ΔV_{AIC} , when scaling the cavity radius at a constant high pressure in comparison with 1 atm. The effect is well interpreted in terms of KB integrals that involve deviations from 1 of the cavity-solvent rdf. These can be positive or negative, so determining locally a negative or a positive contribution to excess volume. At a constant high pressure, well defined hydration shells are maintained even when the cavity can host a solute larger than a fullerene molecule. Hence, examining adsorption at the cavity surface, it seems reasonable to assume a rapid convergence of this quantity to a positive value. On the contrary, at atmospheric pressure, negative adsorption was extrapolated for a very large cavity radius. On the basis of such a different behaviour, adsorption is expected to invert its sign at an intermediate value of pressure. In order to further investigate this point, a systematic study is necessary. This implies a large number of quite expensive simulations, or alternatively, excess volumes can be obtained from Eq. (12), which is convenient when simple models are used to compute the excess chemical potential. On the other hand, the

529 sign of adsorption at the cavity surface extrapolated for an infinite radius can be
530 relevant for their parameterization.

531 The second effect is observed at a fixed cavity radius and mainly consists in the
532 decreasing of excess volumes with increasing pressure in a wide range (1-10000
533 atm) along the isotherm. This is shown in two cases, for cavities that can host
534 spherical solutes approximately as large as a water molecule and slightly larger
535 than a fullerene molecule, respectively. However, for the smaller cavity, simulation
536 results seem to indicate the possibility of a change of slope sign. Fitting the
537 excess volume versus pressure with expressions previously tested on density of
538 pure water enables estimation of its pressure derivative. This can be compared
539 with the value obtained from simulation results of compressibility. Discrepancies
540 can be relatively significant in the case of the smaller cavity. Nevertheless, the
541 comparison shows acceptable consistency if one considers the general problem of
542 computing derivatives with good accuracy.

543 **Supplementary Data**

544 Fig. (S1) and Fig. (S2).

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